**COVER LETTER**

**Submission ID**: 128

**Title**: Interactive Exploration of Ligand Transportation through Protein Tunnels

**Date**: July 17th, 2016

We would like to thank the anonymous reviewers for their helpful comments. We attempted to address all remarks in the revised version of the paper. In this letter, we give detailed responses to all reviewer comments and describe the corresponding changes in our manuscript.

**Reviewer 3 - primary**

1. *There was one significant scientific concern raised by several reviewers, and ask that you do pay attention to that: specifically your choice of trajectory simplifications raises questions regarding its properties and suitability.  There is previous work on trajectory simplification, some quite well studied.  Two of the reviewers pointed out specific works that might be appropriate to consider. It would be helpful to your readers to at least put your algorithm in the context of previous (molecular) trajectory simplification work, or even to provide a choice of simplification algorithms, there are interesting differential benefits between them.*

TODO

1. *From a vis perspective it could use some more work evaluating the correctness of what has been done, and whether there might be alternative solutions that are superior, but, from a biological perspective it's clear that the approach used in the manuscript "works", and having something that works out there for people who are trying to understand molecular ligand/docking trajectories, would be a real plus.*

TODO

1. *One area where I wish the manuscript contained more detail and comparison, is in the simplified trajectory material.  It appears that the simplification mechanism "works", but it's not obvious how well it works, or how robust it is to small variations in the input.  For example, it would be nice to know that the simplification produced from one set of MD runs for a ligand into a pocket, is similar to the simplification produced from a different set of MD runs for the same ligand and pocket.  It would also be nice to have more evidence that the simplification reliably preserves "interesting features" in the trajectory.  Admittedly, there are some challenges to performing these studies, but, whether in this paper or a follow-up, it would be good to give the reader some more information in this area.*

TODO

**Reviewer 1**

1. *There are some minor questions on the design choices (see below). My main question would be about the feedback. Apparently, the biochemists have used the tool. By themselves? What was the major gain? New insight? Or just more efficient? By how much did the efficiency increase?*

TODO

1. *The simplification of the trajectories may not necessarily be the best choice. I would have opted for a multiresolution approach, where small details are succesively omitted, thus effectively applying a low-pass filtering. Then, a simple slider could be used to intuitively and interactively choose the amount of simplification desired.*

TODO

1. *Another parameter is the window chosen for smoothing the scatterplots. Here also the question is how much is desired and whether the control should be given to the user.*

TODO

1. *The analysis starts with an overview of the entire trajectory. This aspect does not scale to very large number of time steps. Any thoughts on this?*

TODO

1. *The Direction parameter sounds like a binary value. I assume it is more like the derivative of the distance, which would make a lot of sense, but it is not so clear from the description.*

TODO

1. *I wonder about the color choices in the overview visualization. WHy were the colors chosen as they are. There is no obvious intuitive interpretation for me and green and blue are hard to distinguish. I actually don't see any blue on my print-out.*

TODO

1. *The description of the coloring of the line charts also remained unclear to me.*

TODO

**Reviewer 2**

1. *This is well written paper and on a specific domain problem. I really don't have any major comments but I'd encourage authors to make their tool and code publicly available for reproducibility and impact.*

TODO

Minor:

1. *Why not use focus+context line graphs as opposed to scatterplots for visualizing attributes along paths. Using scatterplots seems a strange choice, particularly after trajectories are smoothed.*

TODO

1. *The way the terms manual and automatic are used is a bit confusing, given the automatic simplification uses the manual simplification.  Maybe, consider using "interactive simplification" as opposed to "manual simplification" and refer Algorithm 1 directly while discussing automatic simplification*.

TODO

1. *The current formulation of trajectory complexity c(x) suggests that acute alpha's will lead to less complex trajectories, which isn't necessarily accurate. If c(x)is a curvature measure, then what you should care is the deviation of alpha from PI*.

TODO

**Reviewer 4**

1. *While the proposed technique of simplification is interesting, it is not particularly novel and concerns with path simplification in such domains are not clearly addressed by the authors. The expert involvement is minimal and some more insights/comments would have been helpful.*

TODO

1. *Some of the concerns that are not discussed in the paper are related to the simplification algorithm and the presentation of the simplified path. Based on our experience, domain experts are not particularly delighted about the use of simplification. The proposed manual simplification seems to simplify on top of the proposed automated simplification. There may be situations where an expert may want to see more fine grained details and constant simplification throughout may not be the answer.*

TODO

1. *With regards to path/trajectory/line simplification, there is a classic algorithm called the Douglas-Peucker algorithm. I would recommend that the authors take a look at the algorithm and the following improvements on the algorithm.*

*Visvalingam, Mahes, and J. Duncan Whyatt. "The Douglas‐Peucker Algorithm for Line Simplification: Re‐evaluation through Visualization." Computer Graphics Forum. Vol. 9. No. 3. Blackwell Publishing Ltd, 1990.*

*Hershberger, John Edward, and Jack Snoeyink. Speeding up the Douglas-Peucker line-simplification algorithm. University of British Columbia, Department of Computer Science, 1992.*

TODO

1. *The coordinated views that contain bar charts and scatterplots are interesting and definitely useful especially when used in combination such as in Figure 3 and Figure 10.*

TODO

1. *The authors may find the following paper relevant to the visualization in Figure 7 interesting:*

*Rodgers, Peter, Gem Stapleton, and Peter Chapman. "Visualizing sets with linear diagrams." ACM Transactions on Computer-Human Interaction (TOCHI) 22.6 (2015): 27.*

TODO

1. *Overall the paper presents an interesting application of a particular path simplification algorithm to a problem. The domain expert interaction is very minimal. For a paper such as this which is so heavily focused on an application domain, it is critical to have a significant section of the paper discussing domain expert evaluation of the proposed technique. The paper currently has an "Analysis Procedure and Discussion" section, but it is not clear how much interaction the domain expert had and whether any deeper insights were found. Usually, it also helps to show that the technique was applicable in more than one specific case.*

TODO